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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,955	GALILI ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-19,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending.

1. Applicant's election without traverse of Group I, claims 1-9, 12-19 and 26-27 in the reply filed on 06/12/06 is acknowledged.

Claims 10,11,20-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-9, 12-19 and 26-27 read on a method of inducing immune tolerance to an antigen in a mammal, comprising administering an engineered population of white blood cells are under consideration in the instant application.

2. Claim 13 is objected to as being dependent on non-elected claim 11.

Appropriate correction is required.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2-5, 9, 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-5 and 9 are indefinite and ambiguous in the recitation of "and further comprising engineering a population of white blood cells". It is noted that step (a) in the base claim 1 recited "administering an engineered population of white blood cells". In other words, an engineered population of white blood cells should be created prior to the step (a) in the base claim 1.

Claim 26 is indefinite and ambiguous in the recitation of " protein antigen". There is insufficient antecedent basis for this limitation in the claims, since base Claim 1 does not recite "protein antigen".

Claim 27 is indefinite and ambiguous in the recitation of "suppressing the T cell response". It is unclear what type of T cell response applicant intended to suppress. One skill in the art would know that there are exist several types of T cell responses. For example it is unclear if cytotoxic or Th activity or both should be suppressed.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-9, 12-19 and 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing immune tolerance to carbohydrate antigens in mice, comprising administered an engineered population of white blood cells, that expressed α-gal epitope does not reasonably provide **enablement** for a method of inducing immune tolerance to any antigen in any mammals, comprising administering an engineered population of white blood cells that express an antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses *in vivo* studies on KO mice. In said experimental model, an immune tolerance to carbohydrate antigen has been induced when engineered lymphocytes transduced with adenovirus containing α 1,3 GT gene have been administered. Administration of such lymphocytes into KO mice results in tolerization of naïve and memory anti-Gal B cells (see entire document, Examples 1 in particular). .

The specification does not adequately teach how to effectively induce immune tolerance to any antigen in any mammals, by administering an engineered population of white blood cells that express any antigen. Moreover, no animals were used as model system to effectively induce immune tolerance to any antigen. Since there is no animal model studies and data in the specification to show the effectively of inducing immune tolerance to any antigen in any mammal, including human by administering an engineered population of white blood cell, it is unpredictable how to correlate limited results on KO mice with intended *in vivo* use. Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Moreover, Ogawa et al., (Gene Therapy, 2004, Vol.11, pages 292-301) teach that most mammals, including human are immunologically tolerant to α–Gal because their immune system develops in the environment that recognized this antigen as "self". In contrast, KO mice lack a-gal epitope and thus not immunotolerant. **The relevance of this model and method for induction of tolerance to α–gal epitopes in human has first be tested** in monkeys in order to determine whether this phenomenon (induction of tolerance to carbohydrate antigen), which is observed in mice , is also applicable to primates (see entire document, page 299, right column in particular). In addition, in second publication, Ogawa et al., (Blood, 2003, Vol.101, pages 2318-2320) teach that carbohydrate antigens on glycoprotein differ from peptide antigens in that they cannot activate T cells directly because of their protusion from MHC groove. Therefore incompatible carbohydrate antigens on syngernic cells cannot activate T cells (see entire document, page 2318 in particular).

Thus the specification does not teach how to extrapolate data obtained from *in vivo* studies on KO mice wherein an immune tolerance to carbohydrate antigen has been induced to development of effective method of inducing immune tolerance to any antigen in any animal including human , commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of inducing immune tolerance to any antigen in any mammals comprising administering engineered population of white blood cells that expressed an antigen.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed a method of inducing immune tolerance to any antigen in any mammals comprising administering engineered population of white blood cells that expressed an antigen

in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e1) The invention was described in -

(1)an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published of a national application published under section 122(b) only if the international application designation the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

8. Claims 1-4, 9, 12 –16 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 2002/0119571 or WO/01/079300 .

US Patent '571 teaches a method of inducing immune tolerance to an antigen in mammal, comprising administering to said animals engineered population of lymphocytes. (see entire document, Abstract and column 4 and 5 in particular). US Patent '571 teaches that said engineered lymphocytes are obtained by inserting a nucleic acid encoding the portion of the antigen (see column 4 in particular). US Patent '571 teaches the use of retrovirus gene transfer to obtained engineered lymphocytes (see column 4 in particular).

WO 275' teaches a method of inducing immune tolerance to an antigen in mammal, comprising administering to said animals engineered population of lymphocytes. (see entire document, Abstract and page 6, 7 and 52 in particular). WO 275' teaches that said engineered lymphocytes are obtained by inserting a nucleic acid encoding the portion of the antigen (see pages 18 and 19 in particular). WO 275' teaches the use of adenovirus gene transfer to obtained engineered lymphocytes (see pages 19 and 42, 47 in particular).

The references teaching anticipates the claimed invention.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-9 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 2002/0119571 or WO/01/079300 each in view of US Patent 5,879,675.

The teaching of US Patent 2002/0119571 or WO/01/079300 has been discussed, supra.

US Patent 2002/0119571 or WO/01/079300 does not explicitly teach a method of inducing immune tolerance to an carbohydrate antigen, wherein antigen comprises the α-gal epitope , and wherein engineered population of white blood cells are obtained by inserting the nucleic acid encoding said antigen by replication defective adenovirus.

US Patent '675 teaches a method of engineering a population of cells expressing α-gal epitope on its surface, comprising transducing said cells with replication defective adenovirus containing α 1,3 GT gene. (see entire document, columns 8 and 10 in particular). US Patent '675 teaches that said engineered cells can be used to target immune response in mammals.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '675 to those of US Patent 2002/0119571 or WO/01/079300 to obtain a claimed method of inducing immune tolerance to an carbohydrate antigen, wherein antigen comprises the α-gal epitope , and wherein engineered population of white blood cells are obtained by inserting the nucleic acid encoding said antigen by replication defective adenovirus

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because an engineering a population of cells expressing α-gal epitope on its surface, comprising transducing said cells with replication defective adenovirus containing α 1,3 GT gene can be used to target an immune response as taught by US Patent '675. Said replication defective adenovirus containing α 1,3 GT gene can be used to engineered lymphocytes in the method taught by US Patent 2002/0119571 or WO/01/079300 . The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 1-9, 12-19 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bracy et al (Blood, 2000, V.96, pages 3008-3015) in view of US Patent 2002/0119571 and US Patent 5,879,675.

Bracy et al., teach a method of inducing immune tolerance to carbohydrate antigen, comprising administering to a mammal engineered BM cells (see entire document, Abstract in particular). Said engineered BN cells have been constructed by inserting a nucleic acid encoding α-gal epitope using retroviral gene therapy (see entire document, Abstyract in particular). Bracy et al., teach suppressing T cell help response for successful induction of immune tolerance to carbohydrate antigen (see page 3013 in particular). Bracy et al., teach that if possible to achieve even a relatively low but detectable level of α -Gal expressing cells in primates it is likely to be able to eliminate B cells making α -Gal reactive antibodies (see page 3014 in particular).

Bracy et al., do not explicitly teaches a method of inducing immune tolerance comprising administering engineered population of lymphocytes, wherein said lymphocytes are transduced with replication defective adenovirus to express α -Gal epitope on its surface.

US Patent '571 teaches a method of inducing immune tolerance to an antigen in mammal, comprising administering to said animals engineered population of lymphocytes. (see entire document, Abstract and column 4 and 5 in particular). US Patent '571 teaches that said engineered lymphocytes are obtained by inserting a nucleic acid encoding the portion of the antigen (see column 4 in particular). US Patent '571 teaches the use of retrovirus gene transfer to obtained engineered lymphocytes (see column 4 in particular).

US Patent '675 teaches a method of engineering a population of cells expressing α-gal epitope on its surface, comprising transducing said cells with replication defective adenovirus containing α 1,3 GT gene. (see entire document, columns 8 and 10 in particular). US Patent '675 teaches that said engineered cells can be used to target immune response in mammals.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '571 and US Patent 675 to those of Bracy et al., to obtain a claimed method of inducing immune tolerance comprising administering engineered population of lymphocytes, wherein said lymphocytes are transduced with replication defective adenovirus to express α -Gal epitope on its surface.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because base on combine teaching of US Patent '571 and US Patent 675 it would be obvious to engineered a population of lymphocytes that would express α-gal epitope on its surface using replication defective adenovirus. Said engineered population of lymphocytes can be used instead of engineered population of BM cells to induced immune tolerance to carbohydrate antigen as taught by Bracy et al. It is noted that Bracy et al., do not limited their studies to use only engineered BM cells. As has been discussed supra, Bracy et al., teach that if possible to achieve even a relatively low but detectable level of α -Gal expressing cells in primates it is likely that it will be possible to eliminate B cells making α -Gal reactive antibodies. One skill in the art would immediately recognized that induction of tolerance to a α -Gal epitope is not a characteristic limited to BM cells but is a more general phenomenon that can be induced by other cell, for example lymphocytes.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

8/18/06